define that which the Applicants consider to be the invention. In particular, claims 38-42 represent separate claims to the individual sequences listed in the Markush Group of claim 22 and are thus fully supported by the specification. Claim 45 is supported on pages 24-36, page 64, and page 71, lines 6-15. No new matter is added by these claims.

ARGUMENTS

35 U.S.C. 112, Second Paragraph

Claim 22 is rejected under 35 U.S.C. 112, second paragraph as allegedly indefinite for having an improper Markush Group structure and punctuation deficiencies. In response, attorney for Applicants has amended claim 22 to conform with proper formatting and punctuation thereby overcoming the instant rejection. Withdrawal of this rejection is requested.

35 U.S.C. 112, First Paragraph

Claims 3-4, and 22-24 are rejected under 35 U.S.C. 112, first paragraph as allegedly lacking sufficient enablement. In particular, it is alleged that the specification does not provide enablement commensurate with the scope of the claims and that the practice of the invention would require undue experimentation.

It is alleged that aside from teaching SEQ ID NOs:6, 7, 13, 15 and 16, there is no guidance on how to make and use any binding partner of APRIL or AGP-3. Attention is directed to page 64 and page 71, lines 6-15 where an anti-APRIL antibody (*i.e.*, #c19) is described that was not only made, but was also used in a biological assay and shown to reduce the signaling of TACI by inhibiting the formation of antibodies to a prescribed antigen. Accordingly, in contrast to assertions in the Office Action, Applicants have provided specific working examples of binding partners of APRIL that include more than just the sequences noted above. Additionally, there is extensive teaching in the present specification on how to make polypeptides, including antibodies, peptides and muteins, that would function as binding partners of APRIL or AGP-3 (see, for example, pages 24-44 and the working examples on pages 57-71). Some of this extensive teaching is prophetic, however, the Patent and Trademark Office (PTO) itself has stated in the M.P.E.P., quoting a Federal Circuit decision, that prophetic examples are perfectly acceptable.[1]

[1] The Federal Circuit has held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)).

Further, the Office Action also asserts that the specification fails to provide any biochemical information, beyond the sequences listed above, to provide guidance on how to make a binding partner of APRIL or AGP-3 for use in the claimed invention. The Office Action then goes on to state at the bottom of page 3, last full paragraph, that the specification fails to provide guidance on any antibody, peptide, Fc-fusion, etc. This statement seems to broadly reject the entire application, even the working examples, which as noted above, include an antibody example. The Patent Office does not allow this heavy handed type of rejection. Indeed, M.P.E.P. 2164.02 states that 'a single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled.' The sweeping language of the rejection in the Office Action appears to violate this principle.

It is also alleged that it would require undue experimentation to practice the invention. It is noted that the amount of experimentation is not what determines whether it is undue or not, rather it is the nature of the experimentation required, namely, whether it is routine or not.[2] Here, the specification provides detailed working examples of polypeptides and antibodies that function in the claimed invention (pages 57-71). In addition, the specification teaches how one can make various modifications to the polypeptides to develop alternative sequences that function as a binding partner to APRIL, or further AGP-3, and are capable of inhibiting TACI (pages 36-42). The changes can be made by standard mutagenesis, the polypeptides expressed by standard expression systems as disclosed by the present inventors, and the activity of the polypeptides can be tested in the same assays taught by the Applicants in the present specification.

The Office Action further notes that binding partners with different structures would be expected to have differences in activity. This is beyond dispute, however, in order to fit within the confines of the claim language, the binding partner must inhibit TACI activity, BCMA activity or both. Inhibition of these activities was shown to result in amelioration of T cell dependent and T cell independent humoral immune responses in vivo as described in the specification. The measuring of these activities by the assays taught in the specification are routine, and would exclude or include any molecules that lack or have the activity regardless of their structural differences. As there is no rule against defining molecules partly by their

[2] In *Ex parte Jackson*, 217 USPQ 804, the Board of Appeals referring to *Ansul v. Uniroyal*, 169 USPQ 759 (2d Cir. 1971) and *In re Rainer*, 146 USPQ 218 (CCPA 1965) pointed out that: 'determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness having regard to the nature of the invention. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable determination of how to practice a desired embodiment of the invention claimed.'

activity, it is respectfully submitted that the experimentation required to practice the invention is not undue because the generation, production, and screening of variant binding partners of APRIL and/or AGP-3 is routine and the activity of the molecules used in the methods can be routinely measured by standard assays.

Thus, as there are a number of different working examples and extensive teachings with respect to various other binding partners of APRIL and AGP-3, it is respectfully submitted that the present specification is fully enabled for the scope of the claims and the invention can be practiced without undue experimentation and withdrawal of this rejection is requested.

35 U.S.C. 112, First Paragraph

Claims 3-4, and 22-24 are rejected under 35 U.S.C. 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the Applicants had possession of the claimed invention.

The Office Action alleges that the Applicants are in possession of a method of inhibiting TACI activity, BCMA activity or both by the administration of a specific binding partner of APRIL, or further administering a specific binding partner of AGP-3, wherein the binding partner is selected from the group consisting of SEQ ID NOs:6, 7, 13, 15 and 16. In view of this concession, it is not clear how it can then be alleged in the second full paragraph of page 5 of the Office Action, that Applicants did not provide an adequate written description for a specific binding partner that comprises, among other aspects, any sequence recited in claim 22. Clarification is requested.

As described above, the fact that there is a working example of an antibody specific to APRIL that inhibits TACI signaling appears to have been overlooked in the examination of this application. Accordingly, Applicants are in fact in possession of working examples and also extensive prophetic examples of antibodies (*e.g.*, page 64 and page 71 and pages 24-36) that meet the written description guidelines.

In addition, the specification also provides a description of peptides and peptide fusion molecules including structures (*e.g.*, pages 36-37), muteins (*e.g.*, pages 37-42), and also describes amino acid substitutions that can be made in the binding portion of the extracellular domain of TACI or BCMA, based in part on the similarity of these domains to other tumor necrosis factor receptors (*e.g.*, pages 42-44) such that predictive mutations can be made. These various teachings provide adequate written description to the rejected claims. Thus, the Applicants have not only described at length various structures and provided routine assays that can be used to evaluate molecules, Applicants also have provided extensive

working examples of three different molecules, namely, TACI-Fc, BCMA-Fc and an anti-APRIL antibody, that are representative of the genus at issue. Accordingly, it is respectfully submitted that the present specification provides adequate written description for the claimed invention and withdrawal of this rejection is requested.

35 U.S.C. 102(e)

Claims 3-4, and 22-23 are rejected under 35 U.S.C. 102(e) as anticipated by U.S. Patent No. 5,969,102 ("the '102 patent"), evidenced by Ware (J. Exp. Med., 192:F35-F37, 2000). The Office Action alleges that the teachings of the '102 patent inherently encompass the presently claimed invention.

The Federal Circuit has held that inherency requires that the missing descriptive matter is necessarily present in the thing taught in the art and that it would be so recognized by one of ordinary skill in the art. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991). That a thing may or may not be present, is not sufficient to show inherency.[3] Here, the '102 patent suggests that the extracellular domain of TACI can be used to inhibit TACI activity, however, this suggestion is only prophetic and no actual experiments were conducted to demonstrate this inhibition. The assumption that the extracellular domain can be used to inhibit TACI activity is a mere possibility and may not be true. Moreover, the '102 patent does not teach that the extracellular domain needs to be multimerized, as is shown by the present specification. The soluble non-multimerized extracellular domain of TACI would likely have had little inhibitory activity. Accordingly, because the inhibitory activity of the extracellular domain of TACI on TACI activity has not been demonstrated and is only a possibility, it is insufficient to provide the missing elements as alleged in the Office Action.

Furthermore, with respect to claim 22 and its dependent claims which include new claims 38-44 and also new claim 45, the '102 patent fails to teach that the extracellular domain of TACI should be multimerized to be functional and also does not teach that an anti-APRIL antibody can be used to inhibit TACI activity. Accordingly, as claim 22 has been amended to include the requirement that a specific binding partner be a multimer, the '102 patent does not anticipate amended claim 22 or new claims.

In addition, the '102 patent does not teach that the extracellular domain of TACI is a specific binding partner for APRIL, nor does it teach that administration of the extracellular domain of TACI will inhibit BCMA activity. Thus, one of ordinary skill could not have recognized that the extracellular domain of

[3] "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991).

TACI could be used as a specific binding partner for APRIL and could inhibit TACI activity via APRIL signaling, or importantly, that the extracellular domain of TACI could be used to inhibit BCMA activity at the time of filing of the '102 patent but for the teaching of the present specification. Accordingly, the instant reference should not be held to anticipate the present invention because one of ordinary skill would not have recognized the missing descriptive matter as necessarily present.

It is respectfully submitted that the present invention provides novel claims that are not anticipated and withdrawal of this rejection is requested.

35 U.S.C. 103

Claims 22-24 are rejected under 35 U.S.C. 103 as anticipated by U.S. Patent No. 5,969,102 ("the '102 patent"), evidenced by Ware (*J. Exp. Med.*, 192:F35-F37, 2000), and in view of U.S. Patent No. 6,165,745 ("the '745 patent"). The '102 patent teaches that the extracellular domain of TACI could be used to inhibit TACI activity. The '745 patent teaches the production of Fc domain containing polypeptides. It is alleged that because Fc domains extend half lives of some molecules, there would be motivation to combine the two references such that one of ordinary skill would have a reasonable expectation of success, thereby rendering claims 22-24 obvious.

The '102 patent is discussed above and it is submitted that it's failings to make a Section 102 rejection carry over to this rejection. In addition, there is no teaching in the '102 patent to make or use the extracellular domain of TACI as a multimer, or more specifically as a Fc fusion.

Likewise, the '745 patent fails to teach that Fc fusions could be made with TACI, BCMA, APRIL or AGP-3, their extracellular domains or any fragment thereof, other than to generally provide a suggestion that half lives of any fusion molecule with Fc domains can have extended half lives. However, the '745 goes on to state that the Fc domain itself can bind to large numbers of immune cells bearing its receptor in a non-specific manner (see col. 16, lines 10-15). Thus, at the time of these references, it was a significant possibility that in a TACI-Fc fusion, the Fc domain of the fusion polypeptide would interact with immune cells bearing Fc receptors and stimulate them. This would counteract the inhibitory effect of the TACI extracellular domain on TACI signaling, and the molecule would fail as a therapeutic. Thus, the assertion that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention in light of the cited references is in error and withdrawal of this rejection is respectfully requested.

CONCLUSION

It is respectfully submitted that the presently pending claims are now in form for allowance and allowance is earnestly requested. Should a telephone call help facilitate prosecution of this application, the Examiner is encouraged to telephone the undersigned attorney at the number listed below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 22 and 23 have been amended as follows:

22. (Amended) The method of claim 3, wherein the specific binding partner comprises a sequence selected from the group consisting of:

a. the extracellular region of TACI (SEQ ID NO:15),

b. the extracellular region of BCMA (SEQ ID NO:6),

c. the consensus region of TACI (SEQ ID NO:16),

d. the consensus region of BCMA (SEQ ID NO:7), and

e. the TACI/BCMA extracellular consensus sequence (SEQ ID NO:13),

wherein said specific binding partner is a multimer.

23. (Amended) The method of Claim ~~Claims 7, 8, 9 and~~ 22, wherein the specific binding partner is covalently linked to a vehicle.

Claims 38-45 have been added as follows:

--38. (New) The method of Claim 22, wherein the specific binding partner comprises the extracellular region of TACI (SEQ ID NO:15).

39. (New) The method of Claim 22, wherein the specific binding partner comprises the extracellular region of BCMA (SEQ ID NO:6).

40. (New) The method of Claim 22, wherein the specific binding partner comprises the consensus region of TACI (SEQ ID NO:16).

41. (New) The method of Claim 22, wherein the specific binding partner comprises the consensus region of BCMA (SEQ ID NO:7).

42. (New) The method of Claim 22, wherein the specific binding partner comprises the TACI/BCMA extracellular consensus sequence (SEQ ID NO:13).

43. (New) The method of any of Claims 38-42, wherein the specific binding partner is covalently linked to a vehicle.

44. (New) The method of claim 43, wherein the vehicle is an Fc domain.

45. (New) The method of claim 3, wherein the specific binding partner comprises an anti-APRIL antibody.--